Armune BioScience®

APIFINY®

Non-PSA blood test

# PHYSICIAN REFERENCE

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FORM: CT-027 Rev. 04 09/12/17

**What is the basis of the Apifiny Test?**
Apifiny is a cancer specific, non-PSA blood test designed to aid in the risk assessment of prostate cancer. The Apifiny technology is based on the measurement of eight prostate cancer specific autoantibodies in human serum. These autoantibodies are produced and replicated (amplified) by the immune system in response to the presence of prostate cancer cells. The autoantibodies are stable and, because of their amplification, are likely to be abundant and easy to detect, especially at low tumor burdens characteristic of early stage cancer. The use of Apifiny results may supplement other information in the risk assessment for prostate cancer.

The autoantibody markers span a range of biological functions integral to prostate cancer progression. Cell cycle, structure and cellular signaling pathways are all represented.

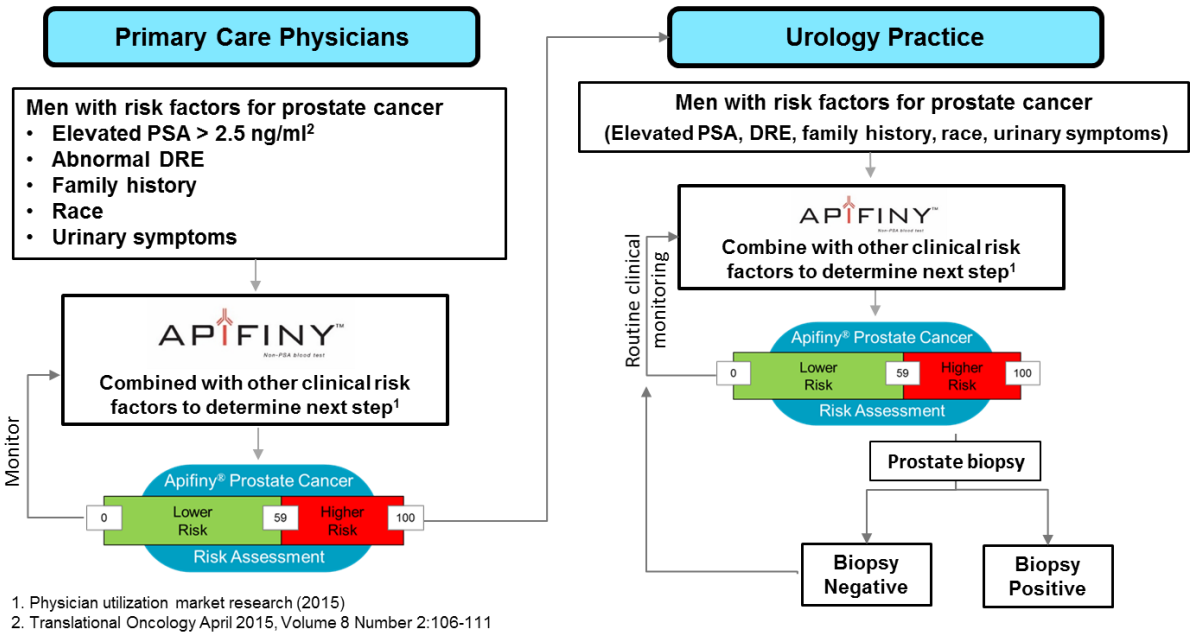
**How do the Apifiny biomarkers relate to each other?**
Statistical analysis shows there is an interdependence among the biomarkers which is further confirmed by their biological functions. Three of the biomarkers are associated with androgen response regulation, and four are related to cellular structural integrity. The eighth biomarker has been associated with prostate cancer progression and a variety of cellular functions ranging from cellular signaling for numerous protein kinases to regulating cell cycle and cellular division. This eighth biomarker appears to be a potential bridge between the biomarkers in the other two general biochemical areas. More information about the biomarkers can be found in Translational Oncology 2015:8 (2):106-11 (Schipper M, Wang G, Giles N, Ohrnberger J. Novel prostate cancer biomarkers derived from autoantibody signatures).

**How is the Apifiny assay performed?**
The Apifiny test process is performed in part using a qualitative immunoassay technique and in part using flow cytometry. The laboratory data generated by these methodologies are then subjected to a proprietary algorithmic analysis that generates a cancer risk score. The Apifiny Test Directory has more information about the assay, test score reference range, laboratory turn-around, and other test details.

**How should Apifiny be used?**
Apifiny is designed to aid in the risk assessment of prostate cancer and should be used in combination with other accepted methods of patient management. Since Apifiny is based on a simple blood draw, it should be easily tolerated by most men. Apifiny score reporting was designed to optimize the identification of patients at lower risk. When combined with other patient information (i.e. PSA level, PSA velocity, DRE, race, family history, etc.) patients with lower risk Apifiny scores may be placed on a routine clinical monitoring program (i.e., semi-annual or annual checkup) with other accepted methods to assess the ongoing risk of prostate cancer. Men with higher Apifiny scores may require a more specific risk assessment plan which may include referral to a specialist and/or a prostate biopsy.

**How do I order Apifiny?**
Download, fill out, and sign the Apifiny Test Requisition Form, ABN Form, and insurance/payment information. If you are using an Apifiny sample collection/mailer kit, the kit will contain Test Requisition and ABN Forms, sample collection materials, and directions. For more information about sample collection, handling, and shipment, refer to the User Guide, available in the Resource Center on Armune's website (www.armune.com), by emailing CustomerService@armune.com, or by calling 844-4Armune (844-427-6863).

**How might Apifiny fit within the clinical management process for my patients?**
Apifiny is designed to aid in the risk assessment of prostate cancer as illustrated below:

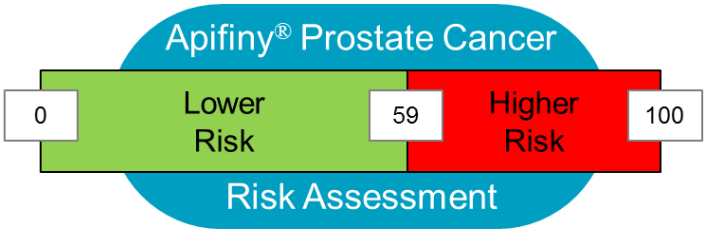



1. Physician utilization market research (2015)
2. Translational Oncology April 2015, Volume 8 Number 2:106-111

**What clinical studies have been completed on Apifiny?**
Two studies have been completed. The first, a biomarker selection / algorithm development study, established the appropriate components for the assay. The second was a clinical validation study.

The assay biomarkers and the classifier algorithm were "locked down" in advance of the validation analysis using entirely independent samples. 519 samples were used in the biomarker selection / algorithm development study and 259 different samples were used in the clinical validation study. Samples were sourced from the University of Michigan, Johns Hopkins University, and Bioreclamation, a commercial sample provider. These studies fully complied with the recommendations of the 2012 report from the Institute of Medicine Committee on Omics-Based Predictive Tests, "Evolution of Translational Omics: Lessons Learned and Path Forward"; National Academy Press, Washington, DC. Results of the studies were analyzed by independent biostatisticians. These two studies were published in Translational Oncology 2015:8 (2):106-11 (Schipper M, Wang G, Giles N, Ohrnberger J. Novel prostate cancer biomarkers derived from autoantibody signatures).

**How are the Apifiny results interpreted?**
Based on the studies and on the design intent of Apifiny, a cut point of 59 was chosen to optimize the identification of patients at lower risk. Scores below 59 are lower risk, while scores at or above 59 are higher risk. Apifiny test score ranges and potential decisions are summarized below. In addition, some interpretive comments and potential "talking points" are provided to support the physician – patient interaction on the discussion of results.




**Lower risk of prostate cancer. Score not consistent with prostate cancer.**

"In the most recent peer-reviewed published study on Apifiny[1], approximately 9 out of 10 men like you, with a score of less than 59, were cancer free."

**Potential clinical decision[2]:** Combine with other clinical information to determine next steps. Continue routine clinical monitoring.

**Higher risk of prostate cancer. Score consistent with prostate cancer.**

"In the most recent peer-reviewed published study on Apifiny[1], approximately 1 out 3 men like you, with a score of 59 or above, had prostate cancer. You may be at higher risk."

**Potential clinical decision[2]:** Combine with other clinical information to determine next steps. Develop an individualized patient management plan and consider a prostate biopsy

1. Translational Oncology, April 2015, Volume 8 Number 2: 106-111
2. Physician utilization market research (2015)

**Is there a range of risk within the lower-risk or higher-risk scores?**
Further analysis of the data from the validation study demonstrates a false positive rate of approximately 20% at the cut point score of 59 and a false positive rate of approximately 4% at scores above 90. More study is required, but this may demonstrate a trend towards greater risk as Apifiny scores increase.

Additional information on the performance of Apifiny is contained in the published validation study (Translational Oncology April 2015: 8 (2):106-11).

**Is there additional information relative to results interpretation?**
Apifiny is a risk assessment tool for prostate cancer based on the presence of eight biological markers known to be associated with an immune system response to prostate cancer. The eight biological markers are not the only markers associated with prostate cancer.

As a result, given the heterogeneity of prostate cancer, not everyone with prostate cancer will possess an immune response to the eight specific markers measured with Apifiny leading to a potential false negative test result.

Also, given the complexity of the human immune system, an individual patient may generate an autoantibody response to one or more of the markers measured by Apifiny and not have prostate cancer, leading to a potential false positive test result. The biological markers measured by Apifiny are known to be associated with an immune system response to prostate cancer. However, these markers could potentially signal another condition not related to prostate cancer.

The Apifiny risk assessment score should always be used in conjunction with other risk factors (age, PSA, PSA velocity, family history, DRE, etc.) to determine the next steps for each individual patient.

The performance characteristics of the test were developed with a validation process that fully complies with the recommendations of the 2012 report from the Institute of Medicine Committee on Omics-Based Predictive Tests, "Evolution of Translational Omics: Lessons Learned and Path Forward" (National Academy Press, Washington, DC). The assay and the classifier algorithm were "locked down" in advance of the validation analysis using entirely independent samples.

**Does a patient's age have an impact on the Apifiny result?**
Armune continues to assess the potential impact of age on Apifiny scores. In the published data on Apifiny, there was no observed impact of age on Apifiny scores (average age was 63 and the maximum age of a study participant was 90). The impact of ages above 90 on an Apifiny score is unknown.

**Does a patient's race have an impact on the Apifiny result?**
Armune continues to assess the potential impact of race on Apifiny scores. In the published data on Apifiny, there was no observed impact of race on Apifiny scores. In addition, in the ongoing clinical assessment of commercial samples of Apifiny, there does not appear to be an impact of race on the scores for Apifiny.

**Do certain drug or "herbal-natural" therapies have an impact on the Apifiny score?**
Armune continues to assess the potential impact of therapies on Apifiny scores. Based on published data, ongoing clinical research, and the company's internal assessment of patient data, Apifiny scores do not appear to be impacted by common therapies for benign prostatic hyperplasia (BPH) such as finasteride or dutasteride, erectile dysfunction therapies, or testosterone replacement therapies. Although there is limited information on the impact of these therapies on Apifiny results, there is no known biological reason why these therapies could impact the result of Apifiny.

For patients on immune-suppressant therapies and/or high dose steroids such as prednisone, Armune recommends that testing with Apifiny be postponed until the course of therapy is complete. In addition, there are studies that indicate the antibiotic doxycycline can potentially cause immunosuppression in some patients. Even though the data is limited, Armune recommends postponing testing with Apifiny for 4-6 weeks after the course of doxycycline is complete.

Additional clinical programs are in development to further assess the potential impact of therapies on Apifiny scores. If healthcare professionals have any questions about a particular therapy and a potential impact on Apifiny, please call Armune at 844-4Armune (844-427-6863).

**Can Apifiny be used to monitor disease progression in men on active surveillance and/or assess the recurrence of disease after local or systemic therapy?**
Apifiny was not developed to be utilized in monitoring disease progression or recurrence of disease. However, in the initial research on Armune BioScience's autoantibody technology published in the New England Journal of Medicine (2005; 353:1224-1235 and Appendix), the autoantibodies demonstrated, in limited patient samples, the potential to be used to assess disease progression and recurrence.

Additional studies are being planned by Armune BioScience and in collaboration with pharmaceutical companies to further assess the potential of autoantibody technology to be used in these important areas.

**Can a urinary tract infection, prostatitis, or recent ejaculation impact an Apifiny result?**
Based on published research on Armune BioScience's autoantibody technology, there has not been an observed impact of these conditions on the scores of Apifiny. Armune's ongoing study and development programs will help to more definitively answer these clinical questions.

**After a negative prostate biopsy, how long should a patient wait before being tested with Apifiny?**
There is currently no evidence to suggest a certain clinical window needs to be maintained after a biopsy before testing with Apifiny. Armune recommends that a physician take into account several clinical factors in negative biopsy patients and test with Apifiny when it is appropriate to provide additional insight into the patient's overall risk assessment for prostate cancer.

**How often should my patients get an Apifiny test?**
Apifiny is the only cancer specific, non-PSA blood test designed to aid in the risk assessment for prostate cancer. Apifiny may be used as part of a routine clinical monitoring program (i.e., semi-annual or annual checkup) to assess a patient's ongoing risk of prostate cancer.

**Should a patient use the results of Apifiny to delay or cancel other tests or treatment?**
No. Apifiny is a risk assessment tool and should be used in conjunction with all the other detection and risk assessment tools at a physician's disposal. Prostate biopsy currently is the primary detection method and should be utilized following a physician's recommendation. Apifiny results may indeed encourage greater compliance with follow up biopsies by men who are identified at higher risk of having prostate cancer.

**Is Apifiny a genetic test?**
Apifiny does not produce genetic information about the patient, and there are no tests for DNA sequences or gene mutations included in the Apifiny assay. The test measures only the level of certain autoantibody proteins in blood serum.

**Who developed the Apifiny test?**
The Apifiny technology is derived from basic research performed at the University of Michigan. Armune BioScience continues to conduct further research and development of the assay for commercial use. Armune BioScience is privately owned.

**What processes are in place regarding ongoing assessment of assay performance?**
The performance characteristics of the test were developed with a validation process that fully complies with the recommendations of the 2012 report from the Institute of Medicine Committee on Omics-Based Predictive Tests, "Evolution of Translational Omics: Lessons Learned and Path Forward" (National Academy Press, Washington, DC). The assay and the classifier algorithm were "locked down" in advance of the validation analysis using entirely independent samples.

Armune BioScience conducts ongoing assessments of Apifiny to ensure the assay performs consistent with how the assay was developed and validated using standard laboratory procedures, quality measures, and in compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88) regulated by the Centers for Medicare & Medicaid Services (CMS).

In addition to standard assessments such as ensuring high and low controls are maintained within range on assay runs, each patient sample is run in triplicate to ensure the accurate assessment of the presence of biomarkers measured by the assay.

As part of ongoing quality procedures within the laboratory, Armune routinely tests commercial samples that were run in prior approved manufacturing lots to ensure the test performs consistently over time and test results are reported in a similar risk range.

Healthcare professionals who would like more information on the lab's quality procedures and testing methods should call Armune at 844-4Armune (844-427-6863).

**How does the Apifiny technology compare with other tests available to assess a patient's risk of prostate cancer?**
Apifiny technology is the only cancer specific, non-PSA blood test available to aid in the risk assessment for prostate cancer. Apifiny has no dependence on PSA, and may directly indicate potential cancer activity in prostate tissue based on the measurement of 8 prostate cancer specific serum autoantibodies created and amplified by the body's own immune system. Apifiny's advantages also include easy blood draw sample collection, low assay rejection rates, and competitive lab turn around and pricing compared to many other alternative tests.

**How can I get more information?**
Review Armune's website (www.armune.com), email CustomerService@armune.com, or call 844-4Armune (844-427-6863) for more information about Armune BioScience, the Apifiny technology, or the Armune BioScience Laboratory.